Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Propafenone hydrochloride 150mg Film-coated Tablets
Propafenone hydrochloride 300mg Film-coated Tablets

(propafenone hydrochloride)

UK/H/1208/01-02/DC
UK licence numbers: PL 20620/0034-5

NRIM Limited

LAY SUMMARY

On 24th December 2010, the MHRA granted NRIM Limited Marketing Authorisations (licences) for the medicinal products Propafenone hydrochloride 150mg Film-coated Tablets and Propafenone hydrochloride 300mg Film-coated Tablets (PL 20620/0034-5). These are prescription-only medicines (POM).

Propafenone is one of a group of medicines called anti-arrhythmic agents and is used for the following:

- To slow down the heart rate and help to regulate the heartbeat
- To treat and prevent arrhythmias (abnormal heart rhythms)

The test products were considered to be generic versions of the reference products Arythmol 150mg and 300mg tablets (PL 00037/0331 and 0332, Abbott Laboratories Limited) based on the data submitted by NRIM Limited.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Propafenone hydrochloride 150mg and 300mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Propafenone hydrochloride 150mg Film-coated Tablets Propafenone hydrochloride 300mg Film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Propafenone hydrochloride
Form	Film-coated tablets
Strength	150 mg, 300 mg
MA Holder	NRIM Limited Marlborough House 298, Regents Park Road Finchley N3 2UA London, United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	UK/H/1208/01-02/DC: Belgium, Germany, Ireland, The Netherlands
Procedure Number	UK/H/1208/01-02/DC
Timetable	End of Procedure: Day 210 – 8th December 2010

Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Propafenone hydrochloride 150mg and 300mg Film-coated Tablets (PL 20620/0034-5) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Propafenone hydrochloride 150mg Film-coated Tablets

Propafenone hydrochloride 300mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150mg / 300mg propafenone hydrochloride

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

For 150mg strength tablets: White to off white, round shaped, biconvex, film coated tablets plain on both sides.

For 300mg strength tablets: White to off-white, round, biconvex, film-coated tablets, with score line on one side and plain on the other side. The tablet can be divided in to equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propafenone is indicated for the prophylaxis and treatment of ventricular arrhythmias.

Propafenone is also indicated for the prophylaxis and treatment of paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter/fibrillation and paroxysmal re-entrant tachycardia's involving the AV node or accessory bypass tracts, when standard therapy has failed or is contraindicated.

4.2 Posology and method of administration

It is recommended that Propafenone therapy should be initiated under hospital conditions, by a physician experienced in the treatment of arrhythmias. The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and blood pressure control. If the QRS interval is prolonged by more than 160msec or the PQ interval is prolonged by more than 20%, the dose should be reduced or discontinued until the ECG returns to normal limits.

Adults
Initially, 150 mg three times daily increasing at a minimum of three-day intervals to 300 mg twice daily and if necessary, to a maximum of 300 mg three times daily.

The tablets should be swallowed whole and taken with a drink after food. A reduction in the total daily dose is recommended for patients below 70 kg bodyweight. The recommended dose is to 5-12mg/kg/day.

Elderly
Higher plasma concentrations of propafenone have been noted during treatment. Elderly patients may therefore respond to a lower dose.

In addition treatment in elderly patients or patients with relevant impairment of ventricular function (left ventricular ejection fraction less than 35%) or structural myocardial disease, should be initiated gradually and with particular caution in small incremental doses. The same applies to maintenance therapy. Any dose increases that may be required should not be undertaken until after five to eight days of therapy.

Children
A suitable dosage form of propafenone hydrochloride tablets for children is not available.

Dosage in impaired liver function
Propafenone is extensively metabolised via a saturable hepatic oxidase pathway. In view of the increased bioavailability and elimination half-life of propafenone, a reduction in the recommended dose may be necessary.

Dosage in impaired renal function
Although the elimination of propafenone and its major metabolite is not affected by renal impairment, propafenone should be administered cautiously.

4.3 Contraindications

Propafenone is contra-indicated in patients with

- Known hypersensitivity to propafenone or to any of the other ingredients.
- Uncontrolled congestive heart failure where left ventricular output is less than 35%, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, uncontrolled electrolyte disturbances (e.g. hyperkalemia or other potassium metabolism disorders), severe obstructive pulmonary disease or marked hypotension.
- Myasthenia gravis.
- Myocardial infarction in the previous 3 months unless life threatening ventricular arryhtmias.

Unless patients are adequately paced (see section 4.4, Special Warnings and Precautions for Use), Propafenone should not be used in the presence of sinus node dysfunction, atrial conduction defects, second degree or greater AV block, bundle branch block or distal block in the absence of an artificial pacemaker.

Minor prolongation of the PR interval and intra-ventricular conduction defects (QRS duration of less than 20%) are to be expected during treatment with propafenone and do not warrant dose reduction or drug withdrawal.

4.4 Special warnings and precautions for use

Electrolyte disturbances should first be treated before treatment with propafenone.

The weak negative inotropic effect of propafenone may assume importance in patients predisposed to cardiac failure. In common with other anti-arrhythmic drugs, propafenone has been shown to alter sensitivity and pacing threshold. In patients with pacemakers, appropriate adjustments may be required. Because of the beta-blocking effect, care should be exercised in the treatment of patients with obstructive airways disease or asthma. Patients with structural heart disease may be predisposed to serious adverse effects.

There is a risk of pro-arrhythmic effects, as with other anti-arrhythmics. Worsening of the ventricular arrhythmias is possible.

For the treatment of ventricular arrhythmias, the patient should be under cardiological surveillance including ECG monitoring and blood pressure control and defribillator facilities should be available.

Treatment stop should be considered with one of the following ECG-changes:

- QRS or QT-interval prolongation with more than 25%,
- PR-interval prolongation with more than 50%,
- QT-interval prolongation with more than 500 msec,
- or a increase in numbers or worsening of the arrhythmias

It is essential that each patient given propafenone hydrochloride be evaluated electrocardiographically and clinically prior to and during therapy to determine whether the response to propafenone hydrochloride supports continued treatment.

There is potential for conversion of paroxysmal atrial fibrillation to atrial flutter with accompanying 2:1 or 1:1 conduction block. As with other class 1C anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse effects

4.5 Interaction with other medicinal products and other forms of interaction

The effects of propafenone may be potentiated if it is given in combination with other local anaesthetic type agents (e.g. pacemaker implantation, surgery or dental work) or agents which depress myocardial activity (e.g. beta blockers, tricyclic antidepressants).

Propafenone has been shown to increase the plasma levels of digoxin and caution should be exercised with regard to digitalis toxicity.

Propafenone has been shown to increase the plasma levels of oral anticoagulants (e.g. warfarin), with an accompanying increase in prothrombin time, which may require a reduction in the dose of oral anticoagulants.

Plasma levels of propafenone may be increased by concomitant administration of cimetidine.

Increased propranolol and metoprolol plasma levels have been observed when these beta-blockers were used concurrently with propafenone. Thus, dose reduction of these beta-blockers may be required. Details of interactions with other beta-blockers are not known.
Coadministration of propafenone hydrochloride with drugs metabolised by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs.

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4, e.g. ketoconazole, cimetidine, quinidine, tropisetron, dolasetron, mizolastine, erythromycin and grapefruit juice may lead to increased levels of propafenone hydrochloride. When propafenone hydrochloride is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Due to the potential for increased plasma concentrations, co-administration of 800-1200mg/day doses of ritonavir and propafenone hydrochloride is contraindicated.

Combination therapy of amiodarone and propafenone hydrochloride can affect conduction and repolarisation and lead to abnormalities that have the potential to be proarrhythmic. Dose adjustments of both compounds based on therapeutic response may be required.

No significant effects on the pharmacokinetics of propafenone or lidocaine have been seen following their concomitant use in patients. However, concomitant use of propafenone hydrochloride and intravenous lidocaine has been reported to increase the risks of central nervous system side effects of lidocaine.

Phenobarbital is a known inducer of CYP3A4. Response to propafenone hydrochloride therapy should be monitored during concomitant chronic phenobarbital use.

There has been a report of the lowering of propafenone levels by rifampicin, via the hepatic mixed oxidase system. This reduction may lead to breakthrough arrhythmias.

Cases of possible interactions with cyclosporin (levels increased with deterioration in renal function), theophylline (levels increased), desipramine (levels increased) have also been reported.

Due to the arrhythmogenic effects of tricyclic and related antidepressants and/or neuroleptics, these drugs may interact adversely when used concomitantly with anti-arrhythmic drugs including propafenone.

Concomitant administration of propafenone hydrochloride and fluoxetine in extensive metabolisers increased the S propafenone C_{max} and AUC by 39 and 50% and the R propafenone C_{max} and AUC by 71 and 50%. Elevated levels of plasma propafenone may occur when propafenone hydrochloride is used concomitantly with paroxetine. Lower doses of propafenone may be sufficient to achieve the desired therapeutic response.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of propafenone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown
Propafenone should not be used during pregnancy unless clearly necessary

Lactation
Propafenone is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with propafenone should be made taking into account the benefit of breast-feeding to the child and the benefit of propafenone therapy to the mother.

4.7 Effects on ability to drive and use machines

Blurred vision, dizziness, fatigue and postural hypotension may affect the patient's speed of reaction and impair the individual's ability to operate machinery or motor vehicles.

4.8 Undesirable effects

The following adverse events have been reported with this or other formulations of propafenone hydrochloride. A cause and effect relationship may not have been established.

Blood and lymphatic system disorders:
Isolated case of leukocytopenia and/ or granulocytopenia or thrombocytopenia; agranulocytosis have been reported.

Immune system disorders:
Allergic reactions, hypersensitivity reactions (manifested by cholestasis, blood dyscrasias).

Metabolism and nutritional Disorders:
Anorexia

Psychiatric disorders:
Anxiety, confusion can occur rarely.

Nervous system disorders:
Dizziness, headache, syncope, ataxia and paresthesia. Very rarely, restlessness, nightmares, sleep disorders and extrapyramidal symptoms vertigo may occur. Rare cases of seizures have been reported.

Eye disorders:
Blurred vision may occur occasionally after a high initial dose.

Cardiac disorders:
A marked reduction in heart rate (bradycardia) or conduction disorders (i.e. atrioventricular or interventricular block) may occur very rarely. Occasionally proarrhythmic effects which manifest as an increase in heart rate (tachycardia), or ventricular fibrillation may also occur.

Vascular disorders Hypotension, including postural hypotension and orthostatic hypotension can be seen occasionally.

Gastrointestinal disorders:
Occasionally, especially with high initial doses, nausea, vomiting constipation, dry mouth, bitter taste, abdominal pain diarrhoea, bloating and retching can occur.

Hepatobiliary disorders:
Rarely, liver abnormalities, including hepatocellular injury, cholestasis, jaundice and hepatitis may occur due to the individual’s hypersensitivity of the hyperergic-allergic type.

Skin and subcutaneous tissue disorders:
Rarely, allergic reaction such as reddening of the skin, rash, itching, urticaria may occur.

Musculoskeletal and connective tissue disorders:
Isolated case of lupus syndrome have been reported, these are reversible on discontinuation of the medicine.

Reproductive system and breast disorders:
Impotence, in some cases, a diminution of potency and a drop in sperm count have been observed after high doses of propafenone. This phenomenon is reversible when treatment is discontinued.

General disorders and administration site conditions:
Rarely fatigue can occur. Chest pain, convulsions following an overdose has been reported very, very rarely. Bronchial spasms may rarely occur on predisposed patients.

Investigations:
Elevated liver enzymes (serum transaminases and alkaline phosphatases

4.9 Overdose

Experience with overdosage is limited. No specific antidote is known. Procedures to enhance drug elimination from the body by haemodialysis or haemoperfusion are unlikely to succeed because of the large volume of drug distribution. The usual emergency measures for acute cardiovascular collapse should be applied. In severe conduction disturbance associated with compromised cardiac function, atropine, isoprenaline or pacemaker therapy may be required. If electrical stimulation is not possible, an attempt should be made to shorten the QRS duration and increase the heart rate with high doses of isoprenaline. Bundle branch block by itself is not an indication for isoprenaline. Hypotension may require inotropic support. Convulsions should be treated with i.v. diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code for propafenone is C01B C03.

Propafenone is a class IC anti-arrhythmic agent.

It has a stabilising action on myocardial membranes, reduces the fast inward current carried by sodium ions with a reduction in depolarisation rate and prolongs the impulse conduction time in the atrium, AV node and primarily, in the His-Purkinje system.

Impulse conduction through accessory pathways, as in WPW syndrome, is either inhibited, by prolongation of the refractory period or blockade of the conduction pathway, both in anterograde but mostly retrograde direction.

At the same time, spontaneous excitability is reduced by an increase of the myocardial stimulus threshold while electrical excitability of the myocardium is decreased by an increase of the ventricular fibrillation threshold.

Anti-arrhythmic effects: Slowing of upstroke velocity of the action potential, decrease of excitability, homogenisation of conduction rates, suppression of ectopic automaticity, lowered myocardial disposition to fibrillation.

Propafenone has moderate beta-sympatholytic activity without clinical relevance. However, the possibility exists that high daily doses (900 - 1200 mg) may trigger a sympatholytic (anti-adrenergic) effect.

In the ECG, propafenone causes a slight prolongation of P, PR and QRS intervals while the QTC interval remains unaffected as a rule.

In digitalised patients with an ejection fraction of 35-50%, contractility of the left ventricle is slightly decreased. In patients with acute transmural infarction and heart failure, the intravenous administration of propafenone may markedly reduce the left ventricular ejection fraction but to an essentially lesser extent in patients in the acute stages of infarction without heart failure. In both cases, pulmonary arterial pressure is minimally raised. Peripheral arterial pressure does not show any significant changes. This demonstrates that propafenone does not exert an unfavourable effect on left ventricular function which would be of clinical relevance. A clinically-relevant reduction of left ventricular function is to be expected only in patients with pre-existing poor ventricular function.

Untreated heart failure might then deteriorate possibly resulting in decompensation.

5.2 Pharmacokinetic properties

Following oral administration, propafenone is nearly completely absorbed from the gastrointestinal tract in a dose-dependent manner and distributed rapidly in the body.

After a single dose of one tablet, bioavailability is about 50%. With repeated doses, plasma concentration and bioavailability rise disproportionately due to saturation of the first pass metabolism in the liver. Steady state is reached after 3 or 4 days, when bioavailability increases to about 100%. Therapeutic plasma levels are in the range of 150 ng/ml to 1500 ng/ml. In the therapeutic concentration range, more than 95% of propafenone is bound to plasma proteins. Comparing cumulative urinary excretion over 24 hours allowed for the calculation that 1.3% of intravenous (70 mg) and 0.65% of oral (600 mg) propafenone is excreted unchanged in the urine, i.e. propafenone is almost exclusively metabolised in the liver. Even in the presence of impaired renal function, reduced elimination of propafenone is not likely, which is confirmed by case reports and single kinetic studies in patients on chronic haemodialysis. Clinical chemistry values did not differ from those of patients with uncompromised kidneys. Refer to section 4.2 for dose recommendation in patients with impaired liver and renal function.

Terminal elimination half-life in patients is 5-7 hours (12 hours in single cases) following repeated doses. A close positive correlation between plasma level and AV conduction time was seen in the majority of both healthy volunteers and patients.

After a plasma level of 500 ng/ml, the PR interval is statistically significantly prolonged as compared to baseline values which allows for dose titration and monitoring of the patients with the help of ECG readings. The frequency of ventricular extrasystoles decreases as plasma concentrations increase. Adequate anti-arrhythmic activity has, in single cases, been observed at plasma levels as low as <500 ng/ml.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity or carcinogenicity.

In reproductive toxicity studies, propafenone was embryotoxic in rabbits and rats at doses 10 and 40 times, respectively, the maximum recommended human dose. In a peri- and post-natal study in rats, propafenone at ≥ 6 times the maximum recommended human dose, increased maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

Intravenous administration of propafenone at doses within the toxic range has caused reversible disorders of spermatogenesis at irregular intervals in monkeys, dogs and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Maize starch
Hypromellose E5
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coat
Talc
Hypromellose E5
Titanium dioxide
Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original carton to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in Aluminium//PVC/PVdC blisters containing 20, 50, 60 (300mg tablets only), 90 (150mg tablets only) & 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20620/0034

PL 20620/0035

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/12/2010

10 DATE OF REVISION OF THE TEXT

24/12/2010

Module 3

Patient Information Leaflet

NRIM

PACKAGE LEAFLET: INFORMATION FOR THE USER
PROPAFENONE HYDROCHLORIDE 150MG FILM-COATED TABLETS
PROPAFENONE HYDROCHLORIDE 300MG FILM-COATED TABLETS

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

THE LEAFLET CONTAINS INFORMATION ON:

1. WHAT PROPAFENONE HYDROCHLORIDE TABLETS ARE AND WHAT THEY ARE USED FOR

Propafenone belongs to a group of medicines called anti-arrhythmic agents.

Propafenone is used for the following:
- To slow down the heart rate and help to regulate the heartbeat
- To treat and prevent arrhythmias (abnormal heart rhythms).

2. BEFORE YOU TAKE PROPAFENONE TABLETS

Do not take propafenone hydrochloride tablets if you:
- are allergic (hypersensitive) to propafenone or any other ingredients in the tablets.
- suffer from heart failure or any heart problems other than abnormal heart rhythm.
- have been diagnosed as having the condition known as myasthenia gravis?

Propafenone hydrochloride tablets are not suitable for children.

Take special care with propafenone hydrochloride tablets and consult your doctor if you:
- are pregnant or planning to become pregnant or breast feeding.
- have an unusually slow heart rate or hypotension (low blood pressure)
- suffer from any breathing problems, such as asthma
- have been told that you have a disturbance in the salts (e.g. sodium or potassium) in your blood

Take special care with propafenone hydrochloride tablets
- If you have a heart pacemaker.

Tell your surgeon or dentist that you are taking propafenone hydrochloride tablets if surgery is planned. It may affect the anaesthetic used.

Taking other medicine
Take special care with propafenone hydrochloride tablets and consult your doctor if you are taking:
- other medicines that affect the activity of the heart such as amiodarone, digoxin, quinidine
- tablets to prevent blood clots (e. g. warfarin)
- antibiotics (e. g. erythromycin or rifampicin)
- any of the group of medicines known as beta-blockers (these are used to treat high blood pressure)
- any antiviral agents (e. g. ritonavir)
- any of the group of medicines known as major tranquillisers, or an antidepressant of the tricyclic or related group (e.g. amitriptyline, dothiepin, desipramine)
- any other antidepressants, such as venlafaxine, fluoxetine, paroxetine
- taking cimetidine (an ulcer medicine)
- cyclosporin (an immunosuppressant, used after transplant operations, or in the treatment of arthritis or psoriasis)
- theophylline (used in the treatment of asthma)
- ketoconazole (an antifungal agent)
- tropisetron or dolasetron (prevention and treatment of nausea and vomiting)
- mizolastine (antihistamine to treat allergy)
- phenobarbital (for epilepsy)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription

Taking propafenone hydrochloride tablets with food or drink
Propafenone hydrochloride tablets should not be taken with grapefruit juice. They should be taken after food, with some water.

Pregnancy and breast-feeding
The safety of propafenone for use during pregnancy has not been established. Hence, it should be taken only if your doctor advises to do so. Please ask your doctor or pharmacist for advice before taking any medicine.

You should not take propafenone hydrochloride tablets if you are breast-feeding

Driving and using machines
Propafenone hydrochloride tablets can cause blurred vision, dizziness, tiredness and low blood pressure in some people. Do not drive, operate machinery or do anything that requires you to be alert until you know how the tablets affect you.

3. HOW TO TAKE PROPAFENONE HYDROCHLORIDE TABLETS

Follow your doctor's directions about when and how to take your tablets and look at the label on the carton. Your pharmacist will also help if you are not sure.

Swallow your tablets with some water. It is best to take them after food.

The number of tablets that you will need to take will be decided by your doctor. This may be between one propafenone hydrochloride 150 mg tablet three times a day to one propafenone hydrochloride 300 mg tablet three times a day.

You may need a lower dose of propafenone hydrochloride tablets if you are elderly, if you have problems with your kidneys or liver, or if you have a low bodyweight.

Propafenone hydrochloride tablets are not recommended for children.

If you take more propafenone hydrochloride tablets than you should
It is important to stick to the dose on the label of the medicine. If you or someone else swallows several of these tablets all together, contact your doctor or nearest hospital emergency department immediately. Always take any tablets left over with you and also the box, as this will allow easier identification of the tablets.

If you forget to take propafenone hydrochloride tablets
If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose do not take a double dose to make up for a forgotten dose, just carry on as before.

If you stop taking propafenone hydrochloride tablets
It is important that you keep taking these tablets until your doctor tells you to stop. Don't stop just because you feel better. If you stop taking the tablets without your doctor's advice, your condition may get worse.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, propafenone hydrochloride tablets can have side effects although not everybody gets them.

Tell your doctor or pharmacist immediately if you experience any of the following:

- Allergic reactions such as skin reddening, itching or a rash. Allergic reactions may affect the liver. Allergic reactions are reversible if the treatment is stopped. These effects are rare.
- Bruise easily or if you develop a very sore throat with a high fever. Treatment may affect the blood. These effects are reversible if the treatment is stopped and have been reported in very rare cases.

The following side effects have been reported: -

Occasionally:
- constipation or diarrhoea
- bloating
- feeling sick
- retching
- vomiting
- loss of appetite
- abdominal pain
- fainting
- ataxia (problems with coordination)
- chest pain
- dizziness
- headaches
- blurred vision
- feeling tired
- dry mouth
- a bitter taste in the mouth
- hypotension (low blood pressure) or unwanted effects on the heart rate

Very rarely:
- restlessness
- nightmares
- sleep disorders
- anxiety
- confusion
- shaking
- stiffness
- seizures
- breathlessness or wheezing.

A reversible drop in the sperm count has occasionally been reported with high doses.

Abnormal liver function blood tests, damage or inflammation of liver cells, and jaundice, have been reported in patients taking propafenone hydrochloride tablets.

Vertigo (spinning sensation), paresthesia (tingling, pins and needles) and lupus syndrome (symptoms include facial rash, joint pain, muscle disorder and fever) have also been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROPAFENONE TABLETS

- Keep out of the reach and sight of children.
- Do not use propafenone hydrochloride tablets after the expiry date, which is stated on the blister and carton. The expiry date refers to the last day of the month.
- Do not store above 25°C. Store in the original carton to protect from moisture.
- Medicines should not be disposed of via wastewater or household waste. Ask you pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What propafenone hydrochloride tablets contain
The name of your medicine is Propafenone hydrochloride 150mg or 300mg film-coated tablets.
The active substance is propafenone hydrochloride. Each film-coated tablet contains 150mg, or 300mg of propafenone hydrochloride. Other ingredients are maize starch, hypromellose E5, microcrystalline cellulose, Croscarmellose sodium, magnesium stearate, talc, titanium dioxide and macrogol 6000.

What propafenone hydrochloride tablets look like and contents of the pack
Propafenone hydrochloride 150mg film-coated tablets are white, round shaped, biconvex, film coated tablets plain on both sides.
Propafenone hydrochloride 300mg film-coated tablets are white to off white, round shaped, biconvex, film-coated tablets with a score line on one side and plain on the other side. The tablet can be divided into equal halves.
Propafenone hydrochloride 150mg film-coated tablets are supplied in Aluminium//PVC/PVdC blisters containing 20, 50, 90 and 100 tablets. Propafenone hydrochloride 300mg film-coated tablets are supplied in Aluminium//PVC/PVdC blisters containing 20, 50, 60 and 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
NRIM Limited Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

This leaflet was prepared in 11/2010

xx-xxx-xxxx

Module 4

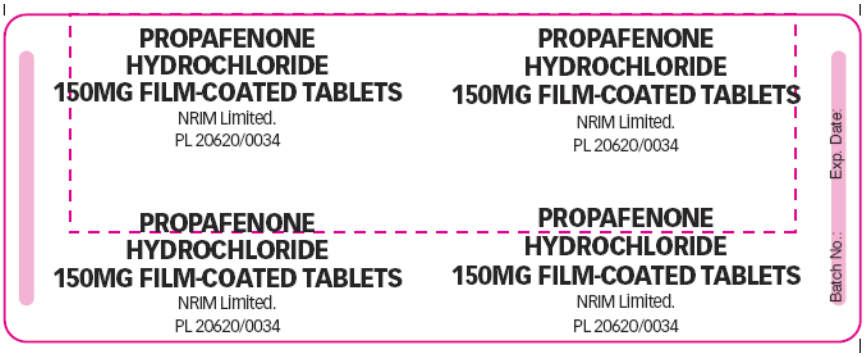
Labelling

Propafenone hydrochloride 150mg Film-coated Tablets – PL 20620/0034

Carton

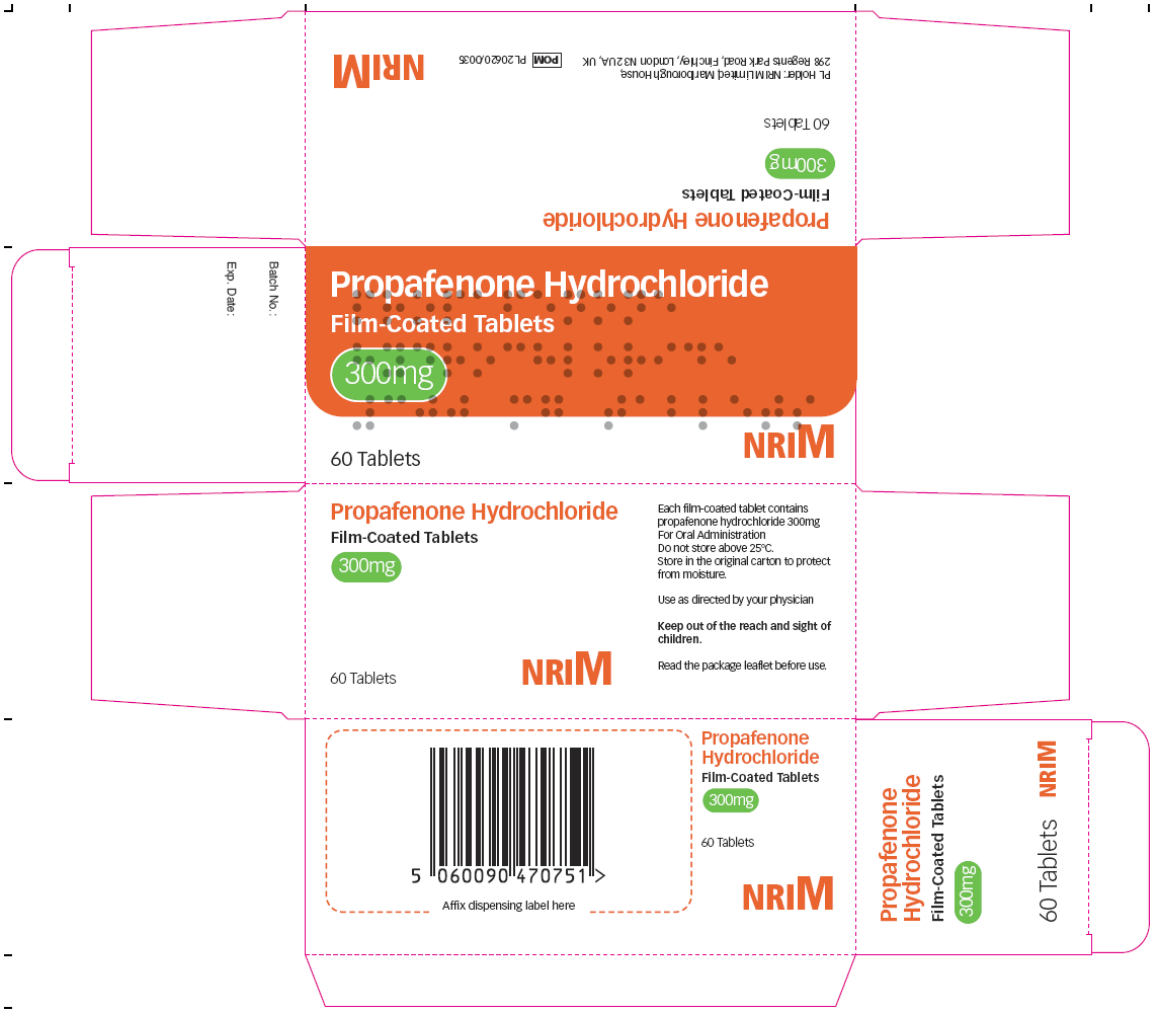
Braille

Blister foil



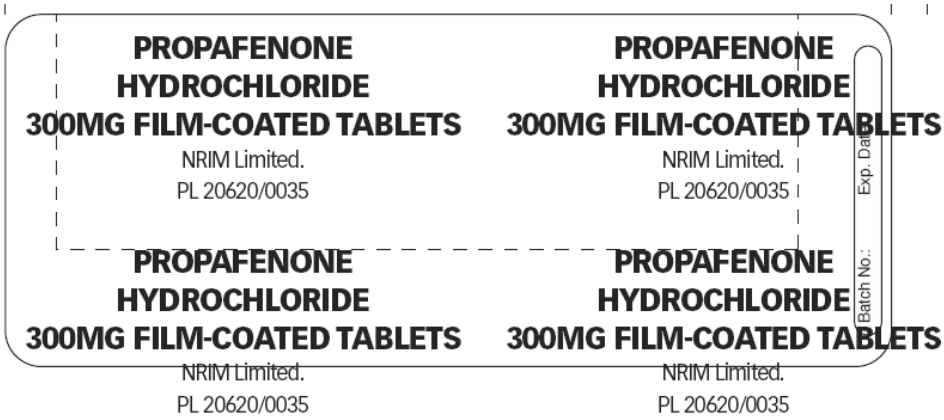
Propafenone hydrochloride 300mg Film-coated Tablets – PL 20620/0035

Carton



Braille

Blister foil



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted NRIM Limited Marketing Authorisations for the medicinal products Propafenone hydrochloride 150mg and 300mg Film-coated Tablets (PL 20620/0034-5; UK/H/1208/01-02/DC) on 24th December 2010. The products are prescription-only medicines.

These are generic applications for Propafenone hydrochloride 150mg and 300mg Film-coated Tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the UK products, Arythmol 150mg and 300mg tablets, originally licensed to Knoll Limited (PL 00169/0015 and 0016) on 21st March 1989. These licences underwent Change of Ownership (CoA) procedures on 5th December 2001 and are currently authorised to Abbott Laboratories Limited (PL 00037/0331 and 0332). The reference products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired. The EU innovator products are Rytmonorm 150mg and 300mg Tablets, first authorised to S.A. Abbott in Belgium on 12th October 1984.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, NRIM Limited applied for Marketing Authorisations for Propafenone hydrochloride 150mg and 300mg Film-coated Tablets in Belgium, Germany, Ireland and The Netherlands.

Propafenone is indicated for the prophylaxis and treatment of:

- ventricular arrhythmias
- paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter/fibrillation and paroxysmal re-entrant tachycardia's involving the AV node or accessory bypass tracts, when standard therapy has failed or is contraindicated

Propafenone is a class IC anti-arrhythmic agent (ATC code – C01B C03) with weak β-adrenoceptor antagonist properties. It has a stabilising action on myocardial membranes, reduces the fast inward current carried by sodium ions with a reduction in depolarisation rate and prolongs the impulse conduction time in the atrium, AV node and primarily, in the His-Purkinje system.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by two bioequivalence studies (one under fasted conditions, one under fed conditions) presented by the applicant comparing the pharmacokinetic profile of the test product, Propafenone hydrochloride 300mg Film-coated Tablets, to that of the reference product, Arythmol 300mg tablets (PL 00037/0332; Abbott Laboratories Limited). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been

provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Propafenone hydrochloride 150mg Film-coated Tablets Propafenone hydrochloride 300mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Propafenone hydrochloride
Pharmacotherapeutic classification (ATC code)	Anti-arrhythmic agents (C01B C03)
Pharmaceutical form and strength(s)	Film-coated tablets 150 mg, 300 mg
Reference numbers for the Decentralised Procedure	UK/H/1208/01-02/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1208/01-02/DC: BE, DE, IE, NL
Marketing Authorisation Number(s)	PL 20620/0034-5
Name and address of the authorisation holder	NRIM Limited Marlborough House 298, Regents Park Road Finchley N3 2UA London, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

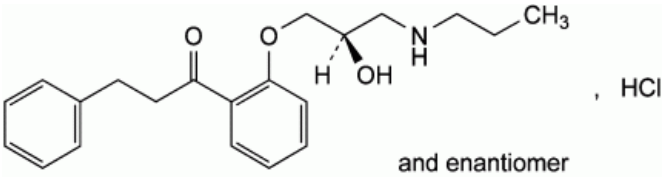
ACTIVE SUBSTANCE

Propafenone hydrochloride

Nomenclature:

INN:	Propafenone hydrochloride
Chemical names:	i) 1-[2-[2-hydroxy-3(propylamino)-propoxy]-phenyl]-3-phenyl-propan-1-one HCl
	ii) 1-[2-[(2RS)-2-Hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylpropan-1-one HCl

Structure:



Molecular formula:	$C_{21}H_{27}NO_3$, HCl
Molecular weight:	377.9 g/mol
CAS No:	34183-22-7
Physical form:	White crystalline powder
Solubility:	Soluble in methanol and in hot water, slightly soluble in alcohol, chloroform and cold water, very slightly soluble in acetone and insoluble in diethyl ether and in toluene

The active substance, propafenone hydrochloride, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in double polyethylene (PE) bags that are then placed inside a fibre drum. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary PE bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended) and comply with Ph. Eur. 3.1.3 “Polyolefines”, and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. Based on the data, a retest period of 60 months has been set with no special storage instructions; this is satisfactory.

MEDICINAL PRODUCT

Description and Composition

Propafenone hydrochloride 150mg and 300mg Film-coated Tablets are presented as white to off-white, round, biconvex, film-coated tablets containing 150mg or 300mg of the active ingredient, propafenone hydrochloride. The 300mg strength tablets have a break-line on one side and can be divided into equal halves.

Other ingredients consist of pharmaceutical excipients, namely maize starch, hypromellose E5, microcrystalline cellulose, croscarmellose sodium and magnesium stearate making up the tablet core; and talc, hypromellose E5, titanium dioxide and macrogol 6000 making up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed products. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, with similar physical and chemical characteristics and bioequivalent to the innovator products, Rytmonorm 150mg and 300mg Tablets (S.A. Abbott) and UK reference products, Arythmol 150mg and 300mg tablets (Abbott Laboratories Limited).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for both strengths of the medicinal product, and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The medicinal products are licensed for marketing in PVC (polyvinylchloride) - PVdC (polyvinylidene chloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 20, 50, 60 (300mg strength tablets only), 90 (150mg strength tablets only) and 100 film-coated tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 4 years has been set with the storage instructions 'Do not store above 25°C. Store in the original carton to protect from moisture'; this is satisfactory.

Bioequivalence Study

Two bioequivalence studies (one fasted, one fed) were presented by the applicant comparing the pharmacokinetic profile of the test product, Propafenone hydrochloride 300mg Film-coated Tablets, to that of the reference product, Arythmol 300mg tablets (PL 00037/0332; Abbott Laboratories Limited).

An evaluation of the bioequivalence studies is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user testing report has been evaluated and is accepted. The labelling text fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Propafenone hydrochloride 150mg and 300mg Film-coated Tablets from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of propafenone hydrochloride, a widely used and well-known active substance. The overview, dated July 2007, cites 24 references from the published literature dated up to 2005. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Arythmol 150mg and 300mg tablets (Abbott Laboratories Limited).

There are no objections to approval of Propafenone hydrochloride 150mg and 300mg Film-coated Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Propafenone is indicated for the prophylaxis and treatment of:

- ventricular arrhythmias
- paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter/fibrillation and paroxysmal re-entrant tachycardia's involving the AV node or accessory bypass tracts, when standard therapy has failed or is contraindicated

The indications are identical to those for the UK reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended posology in adults is an initial dose of 150mg three times daily, increasing at a minimum of three-day intervals to 300mg twice daily and, if necessary, to a maximum of 300mg three times daily.

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the UK reference products and is satisfactory.

TOXICOLOGY

The toxicology of propafenone hydrochloride is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of propafenone hydrochloride is well known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence studies

The applicant presented two bioequivalence studies – one under fasted conditions (Study A), one under fed conditions (Study B) – comparing the pharmacokinetic profile of the test product, Propafenone hydrochloride 300mg Film-coated Tablets, to that of the reference product, Arythmol 300mg tablets (PL 00037/0332; Abbott Laboratories Limited). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products.

The design for both studies was a randomised, open-label, two-treatment, two-sequence, single-dose, four-period replicate crossover oral bioavailability study protocol, performed in healthy adult male human volunteers. Study A was conducted in 35 subjects who had endured a fast of at least 10 hours. Study B was conducted in 38 subjects who had consumed a high fat and high calorie test meal.

A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the dosing days in each group. Blood samples were taken pre-dose (0.0) and at specified time points up to 36.0 hours after administration of test or reference product. Plasma levels of propafenone hydrochloride, its active metabolites, 5-OH propafenone and N-depropylpropafenone, were detected by a validated HPLC-MS analytical method.

The primary pharmacokinetic parameters for the studies are C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product is concluded if the 90% Confidence Intervals (CI) should fall within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Biostudy outcome and results:

Study A – fasted

35 subjects were enrolled in the study; 29 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 6 subjects was satisfactorily justified.

Safety - The two formulations were well tolerated; there were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below.

Pharmacokinetic results for propafenone hydrochloride, 5-OH propafenone and depropyl propafenone for a randomised, open-label, two-treatment, single-dose, four-period replicate crossover study between the test and reference products. n=29 healthy subjects, dosed fasted; t=36 hours. Wash-out period: 7 days

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (X)	Test Product (Y)	Ratio (Y/X) %	
Propafenone hydrochloride				
C_{max} (ng/ml)	235.722	216.024	91.62	82.50-101.76%
AUC_{0-t} (ng.h/ml)	1021.627	952.616	93.25	85.14-102.13%
$AUC_{0-\infty}$ (ng.h/ml)	1131.028	1046.090	92.96	81.37-105.13%
5-OH propafenone				
C_{max} (ng/ml)	173.174	169.786	98.04	90.11-106.68%
AUC_{0-t} (ng.h/ml)	855.197	840.829	98.32	91.57-105.57%
$AUC_{0-\infty}$ (ng.h/ml)	972.216	938.024	96.48	87.44-106.46%
N-depropylpropafenone				
C_{max} (ng/ml)	11.243	10.395	92.45	84.10-101.63%

AUC_{0-t} (ng.h/ml)	77.670	75.628	97.37	86.88-109.13%
$AUC_{0-\infty}$ (ng.h/ml)	91.849	86.492	94.17	83.14-106.65%

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

Discussion

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current recommendations.

Study B – fed

38 subjects were enrolled in the study; 32 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 6 subjects was satisfactorily justified.

Safety - The two formulations were well tolerated; there were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below.

Pharmacokinetic results for propafenone hydrochloride, 5-OH propafenone and depropyl propafenone for a randomised, open-label, two-treatment, single-dose, four-period replicate crossover study between the test and reference products. n=32 healthy subjects, dosed fed; t=36 hours. Wash-out period: 7 days

Parameters	**Geometric Least Squares Mean**			**90% CI (Parametric)**
	Reference Product (X)	**Test Product (Y)**	**Ratio (Y/X) %**	
Propafenone hydrochloride				
C_{max} (ng/ml)	274.469	248.146	90.41	79.62-102.66%
AUC_{0-t} (ng.h/ml)	1128.608	1032.451	91.48	82.25-101.75%
$AUC_{0-\infty}$ (ng.h/ml)	1194.300	1101.094	92.20	83.39-101.93%
5-OH propafenone				
C_{max} (ng/ml)	170.307	166.148	97.56	90.23-105.48%
AUC_{0-t} (ng.h/ml)	944.337	935.470	99.06	94.12-104.26%
$AUC_{0-\infty}$ (ng.h/ml)	985.011	974.728	98.96	94.23-103.92%
N-depropylpropafenone				
C_{max} (ng/ml)	14.706	13.813	93.93	86.34-102.18%
AUC_{0-t} (ng.h/ml)	108.731	102.464	94.24	88.26-100.62%
$AUC_{0-\infty}$ (ng.h/ml)	118.363	112.869	95.36	89.53-101.57%

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

Discussion

For propafenone hydrochloride, the AUC_{0-t} and $AUC_{0-\infty}$ are within acceptable range; however, the C_{max} is just outside the 80.00-125.00% range. The intra-subject variability for test as well as reference product is found to be >30% suggesting inherent high variability of the molecule demonstrated in a replicate design study. This is also corroborated in previous propafenone bioequivalence studies submitted to the US Food and Drug Administration (FDA). Further, the clinical overview provides reasonable evidence that the serum concentrations of this medicinal product are not predictive of anti-arrhythmic effects due to reasons of intra- and inter-individual variability. The bioequivalence of the test and reference products in fed state is therefore accepted.

Conclusion on Bioequivalence

The results of the bioequivalence studies, together with the additional explanations presented, show that the test product and reference product are bioequivalent, under both fasted and fed conditions.

Satisfactory justification is provided for a bio-waiver for Propafenone hydrochloride 150mg Film-coated Tablets. As Propafenone hydrochloride 150mg and 300mg Film-coated Tablets meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence studies on the 300mg strength can be extrapolated to the 150mg strength tablets.

Clinical efficacy

No new data have been submitted and none are required for this type of generic application so long as bioequivalence to the reference products is established. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of propafenone hydrochloride is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of propafenone hydrochloride is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview, dated July 2007, cites 53 references from the published literature dated up to 2005. The CV of the clinical expert has been supplied.

CONCLUSIONS

For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Arythmol 150mg and 300mg tablets (Abbott Laboratories Limited).

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Propafenone hydrochloride 150mg and 300mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's Propafenone hydrochloride 300mg Film-coated Tablets and the UK reference product, Arythmol 300mg tablets (PL 00037/0332; Abbott Laboratories Limited).

As the proposed products, Propafenone hydrochloride 150mg and 300mg Film-coated Tablets, meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence studies on the 300mg strength were extrapolated to the 150mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those of the UK reference products and are satisfactory.

The PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Propafenone hydrochloride 150mg and 300mg Film-coated Tablets are generic versions of the reference products, Arythmol 150mg and 300mg tablets (Abbott Laboratories Limited). Extensive clinical experience with propafenone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome